Atomic Bomb Survivor Studies
History, Dosimetry, Risk Estimation

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Outline

1. **ABCC/RERF background**
   - Immediate effects of the bombs
   - Early studies
   - Major cohorts
2. **Dosimetry**
   - Survivor shielding and location
   - Evolving dose estimates T57D → DS02
   - Dose uncertainties
3. **Risk Estimation**
   - Relative versus absolute risks
   - Describing (smoothing) risk patterns
     - Relative risk and excess rate models
     - Dose response
     - Effect modification
   - Issues
     - Time-since-exposure vs attained age
     - Latent periods
     - Interactions
     - Interpreting site-specific risks

Nature of the bombs

- Hiroshima (Little boy)
  - Unique U^{235} gun-type device
  - 16kt yield
  - Height of burst 600m
  - Hypocenter near city center

- Nagasaki (Fat man)
  - Plutonium implosion device
  - 21 kt yield
  - Height of burst 503m
  - Hypocenter in Urakami valley a residential / industrial area near Nagasaki University about 1.5km north of city center

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Short-term effects

- Result of
  - Blast (50% of energy)
  - Heat (35% of energy)
    - Scorched wood up to 3.5km
  - Radiation (15% of energy)
- Cities largely destroyed
  - Wooden structures burned up to ~2.5km from hypocenter
  - Blast effects apparent over similar distance range
- Populations in areas near hypocenter decimated
  - Hiroshima 110,000 -140,000 deaths
  - Nagasaki 70,000 deaths
  - > 60% mortality within 1km of hypocenter

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Health Effects Research 1945 - 1946

- Japanese research groups
  - Entered cities within days of bombings
  - Carried out various surveys of injuries and deaths
- US research groups
  - Medical teams began arriving in September 1945
  - Efforts directed at cataloging acute radiation effects
- US – Japan Joint Commission
  - Characterize extent of early mortality
  - Nature of acute effects
    - Nausea
    - Epilation
    - Flash burns
    - Bleeding
    - Orapharyngeal lesions
    - Leukopenia

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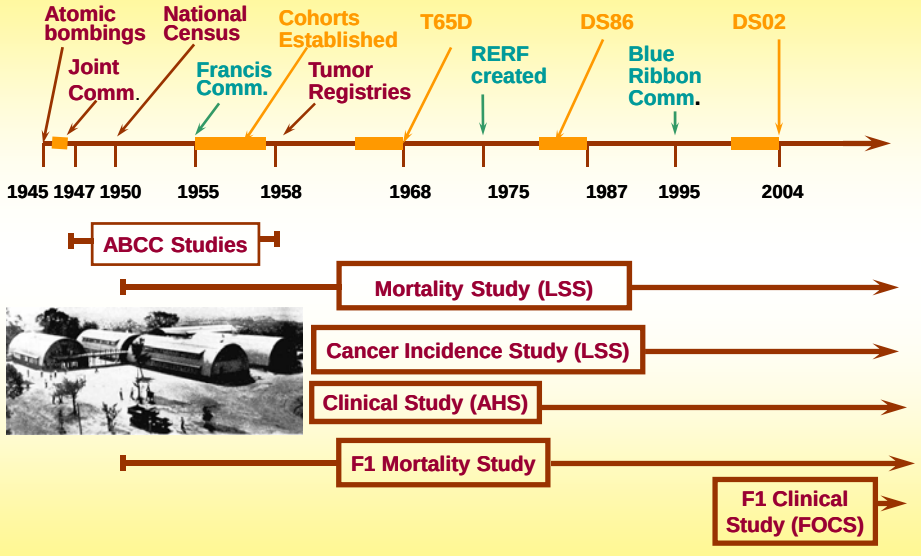
A-bomb Survivor Studies



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Health Effects Research 1947-1955
The Atomic Bomb Casualty Commission (ABCC)

- President Truman authorizes NAS to create and manage ABCC
  - "…undertake a long range, continuing study of the biological and medical effects of the atomic bomb on man."
- Jim Neel, Jack Schull and others develop and implement genetic-effects studies
  - Multiple outcomes
    - Major malformations, premature birth, low birth weight, sex-ratio
  - 72,000 registered pregnancies 1948 -1953
  - Midwife reports, at-birth exams, nine-month exams
  - Results appeared in 1956
    - No apparent effects of radiation exposure (defined by distance and acute effects) on any outcome considered

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Health Effects Research 1947-1955
The Atomic Bomb Casualty Commission (ABCC)

- Leukemia
  - Japanese physicians noticed increase in childhood leukemia cases in late 1940's
  - First published report in 1952
    - Descriptive analyses
    - Ill-defined population
    - No real risk estimates
- 1950 national census
  - ABCC managed data processing
  - Special questionnaire for people who were in or near the cities at the time of the bombs used to define ABCC/RERF Master Sample

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Health Effects Research 1947-1955
The Atomic Bomb Casualty Commission (ABCC)

- Gil Beebe and NAS
  - Developed ideas for cohort-based studies of cancer and other outcomes
    - Paralleled ideas on development do WWII vets follow-up study (Medical Follow-up Agency)
  - Developed ties to Yale and UCLA for recruitment of scientific staff
- Calls for end to ABCC studies
  - Major genetic studies were completed with no compelling evidence of hereditary effects
  - Leukemia excess risk appeared to be declining
  - Studies being carried out in ad-hoc manner
  - Costs for program rising
  - Staff morale low

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Francis Committee
(Thomas Francis, Felix Moore, Seymour Jablon)

- NAS-organized committee to assess what should be done about ABCC research
- Recommendations
  - Reorganized program should continue
  - Unified study plan
    - Focus on fixed cohorts of survivors and their children with internal comparison groups
    - Mortality follow-up
    - Pathology (autopsy) program
    - Clinical studies
    - Highlighted need for dose estimates

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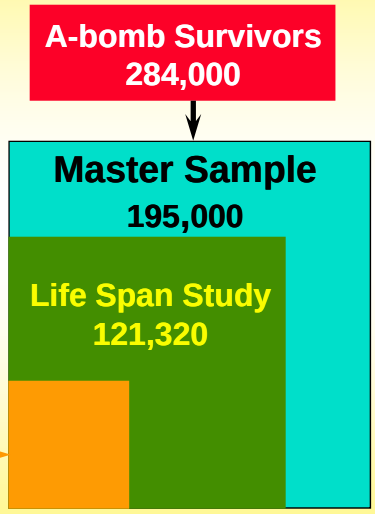
ABCC/RERF Cohorts
Life Span Study (LSS)

Original LSS includes groups of non-military Japanese for whom follow-up data could readily be obtained:

1) All survivors' < 2 km with acute effects
2) Matched group of other survivors < 2 km
3) Matched group of people who were 2.5-10km
4) Matched group of unexposed (not-in-city) individuals

Adult Health Study
22,000



1950 Census

1958-

1958-

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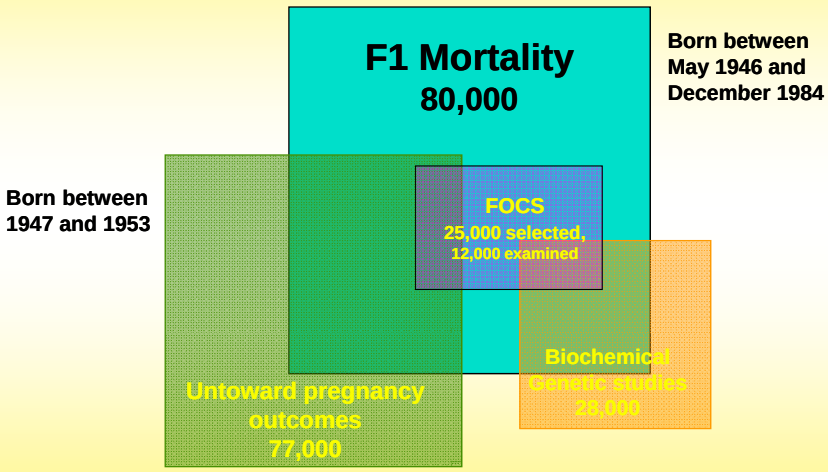
ABCC/RERF - F1 study cohorts



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ABCC-RERF cohorts
In-utero cohort

Pooled IU cohort
3,638 people

- Pooled cohort combines overlapping clinical (1,606 members) and mortality (2,802 members) cohorts.
- Mortality and cancer incidence data are available for all members of the cohort.

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ABCC/RERF Follow-up Programs

- Mortality
  - Based on mandatory nation-wide family registration
  - Updated on a three-year cycle
- Cancer incidence
  - Hiroshima & Nagasaki tumor registries (1958 – present)
  - ABCC pathology program 1958 – 1972
  - Hiroshima & Nagasaki tissue registries 1973 - present
- Leukemia and related disorders
  - Leukemia registry 1950 – 1987
  - Hiroshima & Nagasaki Tumor Registries 1958 – present
- Clinical Examinations
  - Biennial exams
  - 70-80% participation through 25 AHS exam cycles
  - Adapted for use in F1 clinical study (FOCS)
- Mail Surveys
  - 1965 (Ni-hon-san study men), 1968 (women), 1978, 1991, 200?

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ABCC Research 1958 - 1975

- Dosimetry (Auxier, Kerr, Fujita)
  - Development of location and shielding information
  - Introduction of first broadly accepted dosimetry system (T65D)
- Periodic LSS cancer mortality reports (Land, Beebe, Jablon, Kato)
  - Methodological developments & risk estimation
- Clinical studies
  - Cardiovascular disease (Ni-Hon-San), Non-specific aging
  - Thyroid and skin diseases
  - Radiation cataract
- Cytogenetics studies (Awa)
- In-utero
  - Physical growth and development
  - IQ
  - Mortality
- F1
  - Leukemia incidence
  - General mortality

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RERF Research 1975-1995

- Improved LSS cancer mortality reports
  - Dose–response shape & effect modification
- Solid cancer and leukemia incidence reports
- Breast cancer incidence studies (Land, Tokunaga)
  - Precursor to more recent site-specific incidence papers
- F1 studies
  - Biochemical and cytogenetics studies
- In-utero
  - Mental retardation, School performance
  - Cancer mortality, leukemia incidence

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RERF Research 1995 - present

- Increasing emphasis on site-specific cancer incidence
- Emerging evidence of non-cancer mortality risks
- Analyses of clinical data
  - Noncancer disease morbidity
  - Longitudinal laboratory measurements (blood pressure, cholesterol, inflammatory markers)
  - Cataracts

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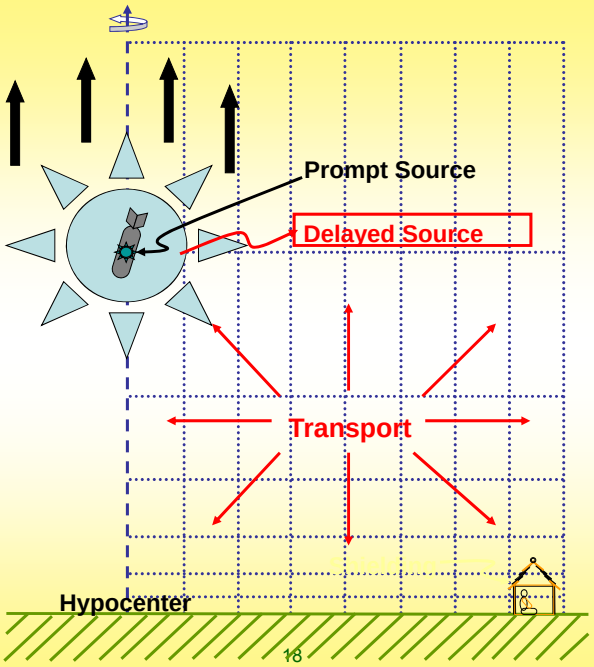

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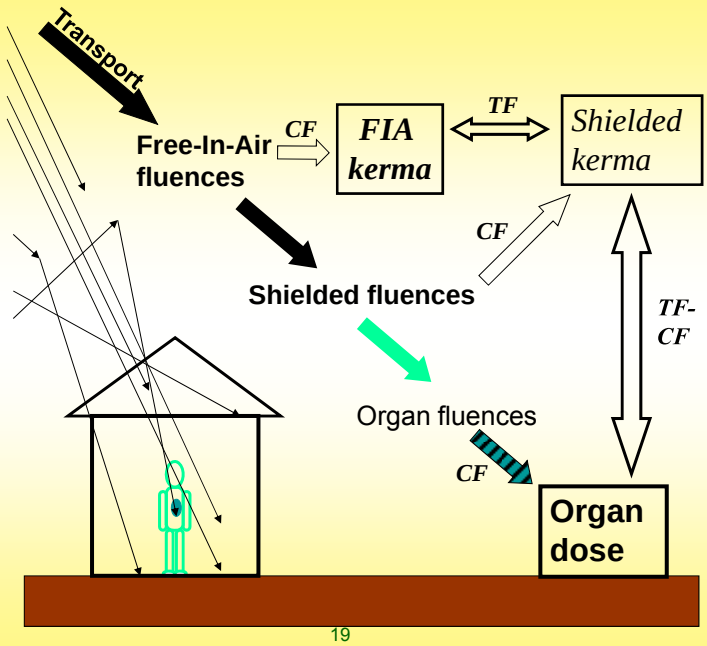

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Dosimetry

- Location
  - Specified as coordinates on fairly crude US army maps
    - Sought corroboration of location
    - Recorded to nearest 10m in each coordinate if detailed shielding history obtained and nearest 100m for others
- External Shielding
  - Crude shielding category information available on virtually all people of interest
  - Detailed shielding histories for most survivors within 1.6km in Hiroshima and 2 km in Nagasaki
- Self shielding (organ dose)
  - Available for survivors with detailed shielding histories

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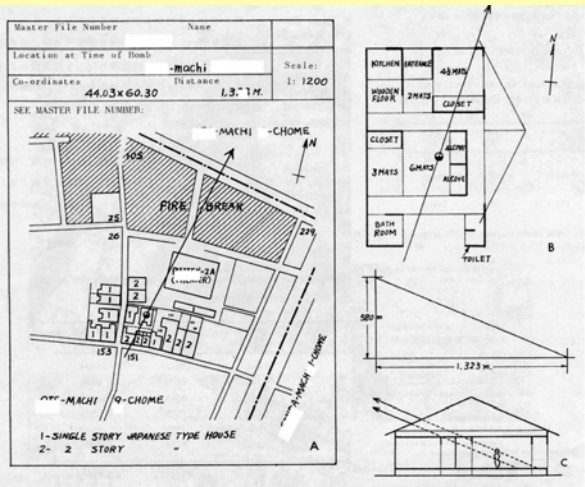
Sample Shielding History



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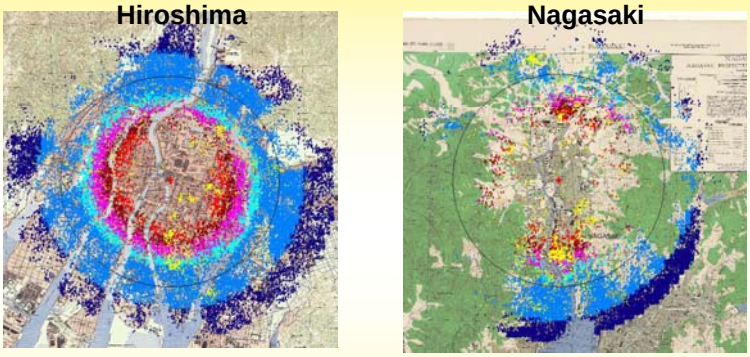
LSS Survivors within 3 Km



✚ Hypocenter

Dose (mSv)

- < 5
- 5 – 100
- 100 – 200
- 200 - 500
- 500 – 1000
- 1000 +
- unknown

*** LSS: Life Span Study Cohort**

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Dosimetry History

- Early analyses based on categories defined by distance and acute effects
- Tentative 1957 Dosimetry (T57D)
  - Declassified gamma and neutron “air dose” curves by city
  - Crude allowance for shielding
  - Never used for routine analyses
- T65D
  - City-specific gamma and neutron equations for free-in-air kerma versus distance
  - Limited validation from physical measurements (TLD and Co^{60} activation)
  - External shielding effects described as transmission factors
    - House shielding based on nine-parameter model or average values
    - Globe method (look at shadows in model conditions)
    - Nagasaki factory model

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Dosimetry History

- DS86
  - Motivated by concerns about T65D neutrons
  - Involved review of all aspects of bombs, transport, and shielding
  - Used (then-)modern monte-carlo transport codes
  - Provided shielded kerma and dose estimates for 15 tissues with up to six components
  - Reduced neutron doses (especially for Hiroshima) and transmission factors for houses
  - Some validation by measurements, but some questions about neutron doses lingered

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Dosimetry History

- DS02
  - Possibility of increased Hiroshima neutrons at distance received much attention
  - Extensive program of validation measurements and inter-laboratory comparisons
  - Additional review of bomb parameters
    - Hiroshima yield increased from 15 to 16kt
    - Hiroshima height of burst 580 → 600
    - Nagasaki prompt gamma per kt increased by 9%
  - Further review of shielding effects
    - New models for large wooden buildings and Nagasaki factories
    - Allowance for distal terrain shielding

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Dose Uncertainty

- Uncertainty in survivor dose estimates recognized from the beginning, but
- Until recently little effort to allow for or assess impact of uncertainty on risk estimates
- Types of uncertainty
  - Shared errors – yield, shielding parameters etc.
  - Grouping (Berkson) errors
  - Error in individual location / shielding information (classical error)
- Currently doses are corrected for 35% random errors using a regression calibration method in which D_{est} is replaced by $E(D_{true}|D_{est})$
- Can expect further advances in next few years
  - More use of biodosimetry data
  - Explicit consideration of Berkson, classical, and shared error effects

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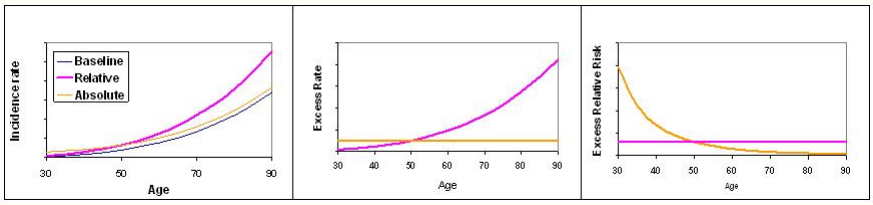
The Old Debate
Relative versus Absolute Risks

- Do excess risks increase or become relatively less important as time goes by?



- By early 1980's it was agreed that relative risk provided a better description
- Time-constant (excess) relative risk became standard risk summary

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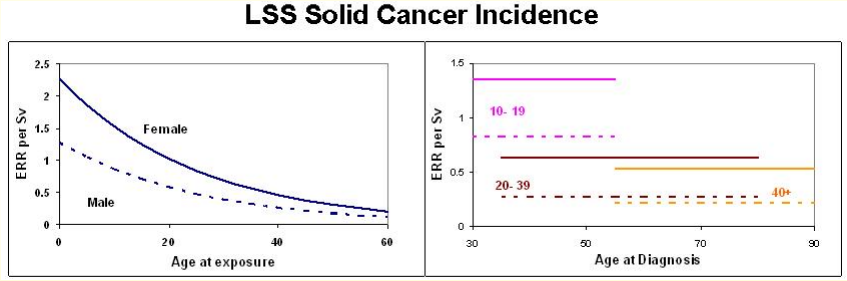
Evolving Understandings
Excess Risk is Not a Number

- (Relative) risk depends on gender and age at exposure



- Are excess relative risks constant in attained age (time) given age at exposure and sex?
- How should we interpret gender differences in the ERR?

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Evolving Understandings
Describing Excess Risks

Excess relative risk (ERR) model

$$\lambda_o(a,s,b)[1+\rho(d)\varepsilon_R(s,e,a)]$$

Excess absolute rate (EAR) model

$$\lambda_o(a,s,b)+\rho(d)\varepsilon_A(s,e,a)$$

$\lambda_o(a,s,b)$	Baseline (zero dose) risk function *a* age at risk; *s* gender; and *b* birth cohort
$\rho(d)$	Dose-response shape , e.g. linear, linear-quadratic, threshold, …
$\varepsilon(s,e,a)$	Effect modification function *e* age at exposure

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Evolving Understandings
ERR versus EAR description

- ERR and EAR are (in principle) equivalent descriptions of the excess risk

$$\varepsilon_R(s,e,a)=\frac{\varepsilon_A(s,e,a)}{\lambda_0(a,s,b)}$$

- Both ERR and EAR descriptions are important
- ERR and EAR provide complimentary information
  - Patterns in ERR effect modifiers may reflect factors such as gender and birth cohort effects in baseline rates
- Description may be simpler or more informative on one scale than the other

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Describing Gender and Age-Time Effects

- Smoothing the excess is essential to understanding
  - Subset analyses have little power
  - Uncertainty can make it difficult to see patterns
- Requires choice of variables and model form
  - RERF analyses generally based on log-linear descriptions *(when there is enough data)*

$$\varepsilon(s,e,a) = \exp(\beta_s + \theta e + \gamma \log(a))$$

$\exp(\beta_f) / \exp(\beta_m)$	female:male excess (relative) risk ratio
$\exp(10\ \theta)-1$	% change per decade increase in age at exposure
γ	power of age at risk

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Describing Gender and Age-Time Effects

- Extensions of basic model possible
  - Sex-dependent age and age at exposure effects
  - Other functions of age and age at exposure
- However, available data usually too limited to support such detailed descriptions

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LSS Solid Cancer Incidence 1958-94

By age at exposure					
Age at exposure	People	Person years	Cases	Estimated Excess	AR%*
Male					
0-19	21,571	632,341	2,409	150	13%
20-39	8,522	229,518	2,569	86	8%
40+	12,809	178,419	2,991	61	5%
Total	*42,902*	*1,040,278*	*7,969*	*297*	9%
Female					
0-19	24,169	755,387	2,186	240	24%
20-39	21,561	679,452	4,423	233	11%
40+	16,795	289,614	2,870	83	6%
Total	*62,525*	*1,724,453*	*9,479*	*556*	13%
Total	***105,427***	***2,764,731***	***17,448***	***853***	***11%***

By colon dose					
Colon Dose	People	Person years	Cases	Estimated Excess	AR%
< 0.005	60,792	1,598,944	9,597	3	0%
- 0.1	27,789	729,603	4,406	81	2%
- 0.2	5,527	145,925	968	75	8%
- 0.5	5,935	153,886	1,144	179	16%
- 1	3,173	81,251	688	206	30%
- 2	1,647	41,412	460	196	43%
2+	564	13,711	185	111	60%
Total	***105,427***	***2,764,732***	***17,448***	***853***	***11%*** *

* Attributable risk % for people with doses > 0.005 Gy

- Information on gender and age-time patterns depends (only) on radiation-associated ("excess") cases
- Excess cases not explicitly identified
- Number of relevant cases is relatively small, especially for specific sites

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LSS Leukemia Mortality 1950-2000

By age at exposure					
Age at exposure	People	Person years	Cases	Estimated Excess	AR%*
Male					
0-19	16,827	783,098	60	26	58%
20-39	6,411	229,330	49	12	42%
40+	12,449	227,441	47	13	41%
Total	*35,687*	*1,239,869*	*156*	*52*	48%
Female					
0-19	18,569	891,288	42	16	51%
20-39	16,750	702,633	57	17	41%
40+	15,605	350,566	41	9	36%
Total	*50,924*	*1,944,487*	*140*	*43*	43%
Total	***86,611***	***3,184,355***	***296***	***94***	***46%***

By marrow dose					
Marrow Dose	People	Person years	Cases	Estimated Excess	AR%
< 0.005	36,502	1,342,168	89	0	0%
- 0.1	30,898	1,135,582	69	4	6%
- 0.2	6,006	223,701	17	4	25%
- 0.5	6,993	256,584	31	13	41%
- 1	3,512	129,053	27	18	68%
1+	2,700	97,267	63	55	87%
Total	***86,611***	***3,184,355***	***296***	***94***	***46%****

* Attributable risk % among survivors with marrow dose > 0.005 Gy

- Despite smaller number of excess cases, a considerably larger proportion of the cases are radiation-associated

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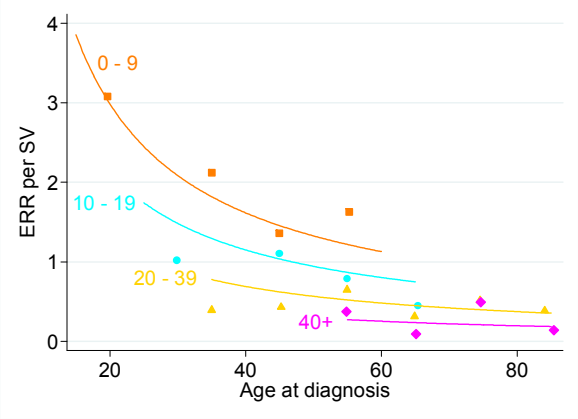
LSS Solid Cancer Mortality 1950 – 2000
Excess Relative Risk Temporal Patterns



Age at exposure

-29% per decade

(90% CI -39%; -18%)

Attained age

$Age^{-0.9}$

(90% CI -1.5; -0.2)

Gender *

M: 0.29 *(90% CI 0.21; 0.39)*
F: 0.58 *(90% CI 0.42; 0.68)*
F:M: 1.9 *(90% CI 1.4; 2.7)*

* ERR per Sv at age 70 following exposure at age 30

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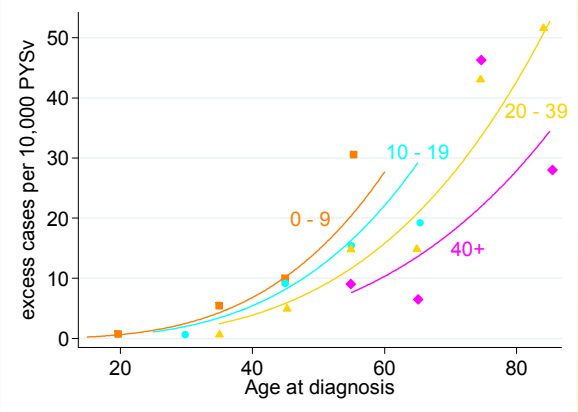
LSS Solid Cancer Mortality 1950 – 2000
Excess Rate Temporal Patterns



Age at exposure

-20% per decade

(90% CI -30%; -10%)

Attained age

$Age^{3.5}$

(90% CI 2.9; 4.1)

Gender *

M: 26 *(90% CI 18; 34)*
F: 28 *(90% CI 23; 34)*
F:M: 1.1 *(90% CI 0.8; 1.6)*

* Excess cases per 10000 PY at age 70 following exposure at age 30

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Related Issues
Time-Since-Exposure

- Solid cancer
  - LSS data suggest that largest risks occur late in life regardless of age at exposure
  - EAR TSE model fits worse than attained-age model without an agex-by-TSE interaction
- Leukemia
  - TSE models motivated by EAR decrease and the belief that the excess disappeared after 15 to 20 years
  - TSE models involve significant agex-by-TSE interaction
  - Attained age models provide comparable fit without need for interaction

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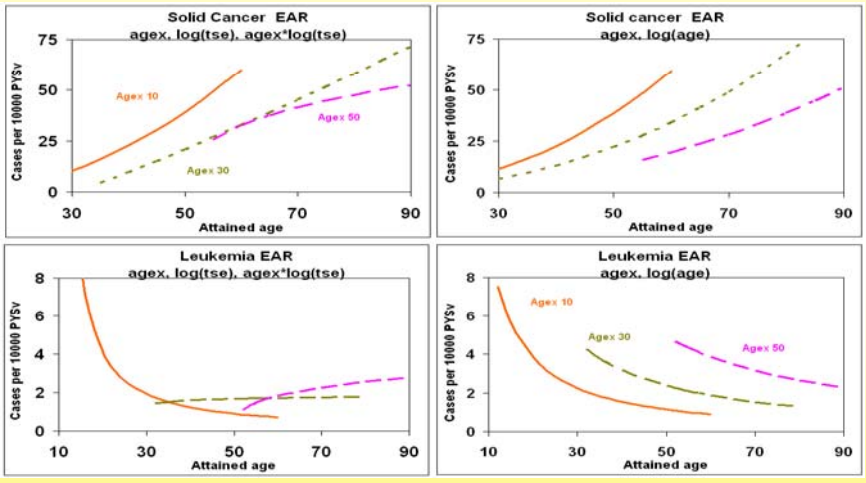
Comparison of Time-Since-Exposure and Attained-Age Fits



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Related Issues
Time-Constant ERR models

- LSS data clearly suggest that the ERR varies with attained age (time since exposure)
- It is difficult to conceive of a radiation carcinogenesis mechanism that would lead to time-constant increases in the ERR

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Related Issues
Latency

- Concept of limited usefulness
  - Definition is vague
  - Dose response implies reductions in the expected time from exposure to tumor
  - Minimum latency period is at least time from the final conversion into a malignant cell until diagnosis or death but could be longer
    - Mayak and early a-bomb survivor data indicate that radiation-associated leukemia deaths can occur within two to three years of exposure
    - LSS solid mortality data provide some suggestion of elevated risk 5 to 10 years after exposure for older cohort members
- Better to simply describe age-time patterns

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Radiation and Other Risk Factors Confounding

- Other factor affects risk of outcome
- Radiation exposure/dose correlated with level of other risk factor
- Without adjustment apparent radiation effect estimate is distorted
- Likelihood of serious confounding is likely to be decreased if individual dose estimates are available
- Example: radiation, smoking, and lung cancer
  - Smoking is a major cause of lung cancer
  - If radiation exposure/dose and smoking are correlated failure to adjust for smoking will bias the radiation risk estimate
  - Magnitude of bias depends on size of smoking effect and magnitude of correlation between radiation and smoking

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Radiation and Other Risk Factors Interactions

- Radiation effect differs for different levels of some risk factor
  - Both radiation and other factor alter risk of outcome
- Unadjusted radiation effect estimate depends on distribution of other risk factor
- Model joint effect of radiation and other risk factor
  - Requires considerable amount of data
  - Characterization of nature of interaction is quite difficult
- Example: radiation, smoking and lung cancer
  - Smoking is a known strong causal factor for lung cancer
  - Radiation is also a causal factor
  - What is nature of the joint effect of radiation and smoking on excess risk

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Radiation and Other Risk Factors Interaction Models

- Focus on relative risk models
  - ERR models are the most natural way to describe interactions
- Simple models
  - Additive: Rate = BKG (1 + ERR_{smk} + ERR_{rad})
    - ERR_{smk} and ERR_{rad} are relative to rates for unexposed non-smokers
    - Smoking (BKG* ERR_{smk}) and radiation (BKG* ERR_{rad}) **excess rates** are independent
  - Multiplicative: Rate = BKG(1 + ERR_{smk}) (1 + ERR_{rad}) = BKG(1 + ERR_{smk} + ERR_{rad} + $ERR_{smk}ERR_{rad}$)
    - ERR_{rad} (ERR_{smk}) is the same for all levels of smoking (radiation exposure)
    - ERR_{rad} (ERR_{smk}) is relative to rates that include smoking (radiation) effect

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Radiation and Other Risk Factors Interaction Models

- Simple generalized interaction model
  - Rate = BKG (1 + ERR_{smk} + ERR_{rad} + θ ERR_{smk} ERR_{rad})
    simple additive (θ=0) and multiplicative (θ=1) models are special cases
- Generalized additive model
  - Rate = BKG (1 + ERR_{smk} + ERR_{rad} *f(smk))
    f(smk) is a function of smoking behavior such that f(smk)=1 for non-smokers
- Generalized multiplicative model
  - Rate = BKG (1 + ERR_{smk})(1+ ERR_{rad} *f(smk))

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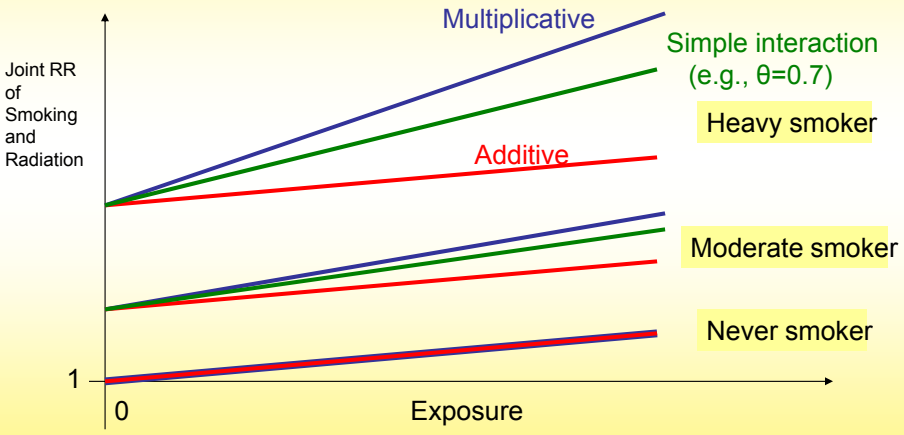
Models
Additive or Multiplicative ?



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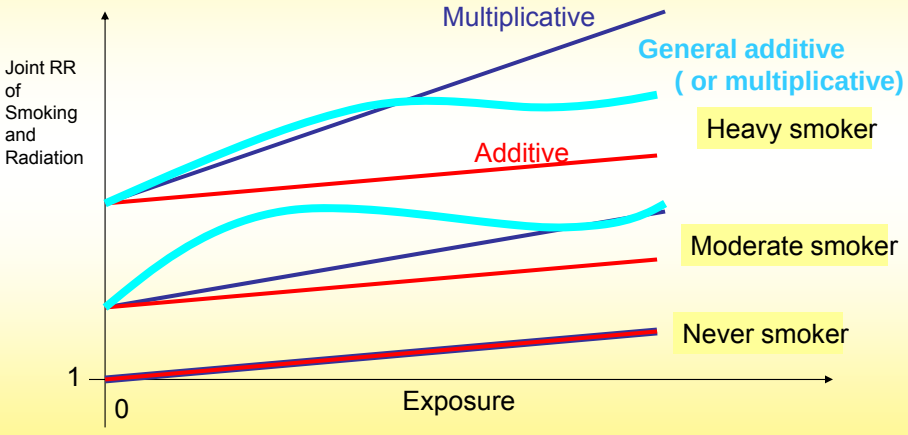
Models
Additive, Multiplicative or General?



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Lung Cancer Rate Model

- Background rates (unexposed never smokers)
  - Sex-specific log quadratic spline in log age
  - Additional effects for *year of birth*, *sex*, *city*, *location (in city or not)*
- Radiation ERR
  - $ERR_{rad} = \beta_{sex}\ dose \cdot age^{\gamma} \cdot \exp\{\alpha\ agex\}$
- Smoking effect
  - Dependent on smoking duration (*dur*), intensity(*pkday*), time since quitting (*tsq*) and pack-years (*pkyr* = *dura* · *pkday*)
  - $ERR_{smk} = \delta_{sex}\ pkyr\ \exp\{\zeta pkday + \eta \log(dur) + \varphi \log(1+tsq)\}$
- Generalized interaction
  - $ERR_{rad(smk)} = ERR_{rad} \cdot \exp(\psi_1\ pkday + \psi_2\ pkday^2)$

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Result Smoking Excess Risk

	ERR/40packyr		Pack/day	Duration (power)	Years since quitting (power)
	Male	female			
Smk Only	2.72	4.07	-0.40	0.74	-0.36
Additive	2.79	4.49	-0.37	0.78	-0.35
GenAdditive	2.63	3.95	-0.27	0.87	-0.35
Multipve	2.73	3.86	-0.40	0.72	-0.35
GenMultipve	2.77	3.69	-0.25	0.74	-0.35

ERR/40packyr= Smoking ERR for those who smoke a pack a day for 40 years

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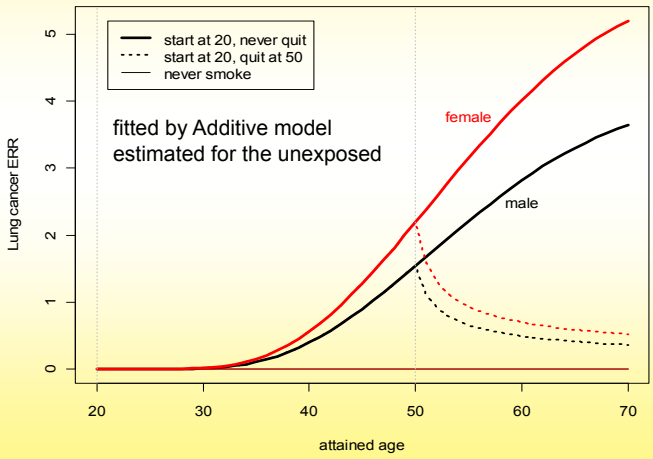
Result
Smoking Excess Risk (Cnt'd)



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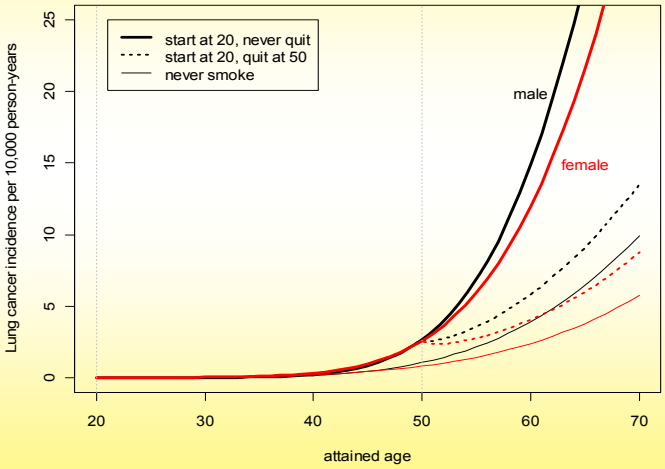
Result
Rates for Smokers / Non-smokers



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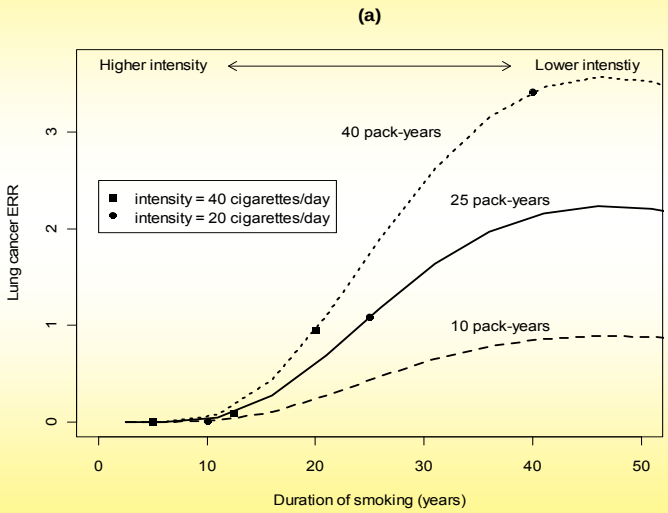
Result
Duration & Intensity Effects



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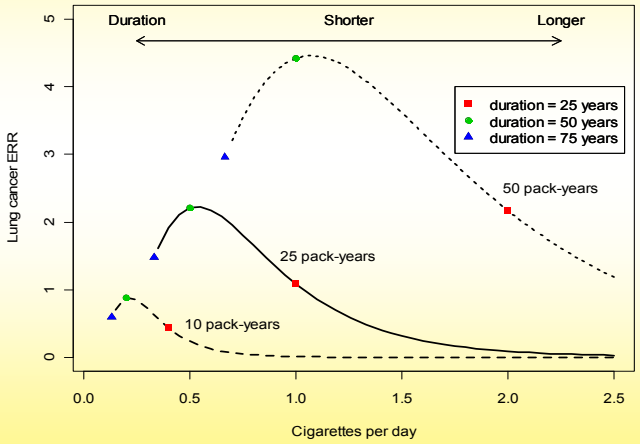
Result
Duration & Intensity Effects



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Result
Radiation Excess Risk

	ERR/Gy	Attained age (power)	Age at exp %change/10yrs	FM Ratio
Rad Only	0.80	-1.85	23.33	4.15
Additive	1.03	-2.36	20.34	1.85
GenAdditive	0.64	-2.81	44.07	3.79
Multipve	0.68	-2.25	27.60	3.74
GenMultipve	0.57	-2.59	32.40	3.45

ERR/Gy= sex averaged linear dose response for those with attained age at 70 and exposed age at 30

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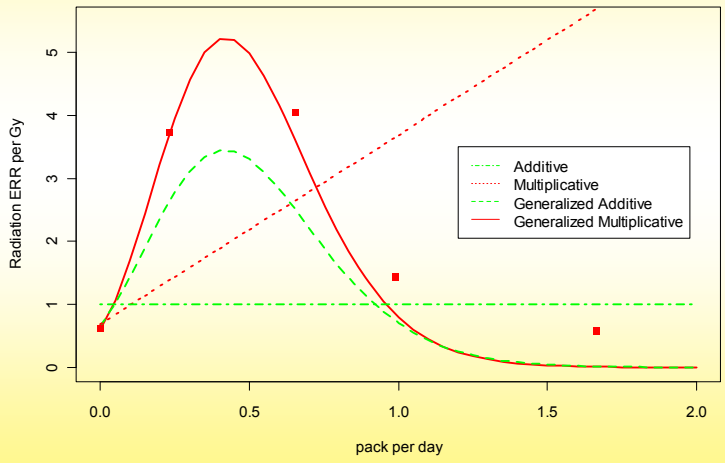
Result
Smoking-Radiation Interaction



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LSS Radiation and Smoking in the LSS Summary

- Smoking effects on lung cancer were modeled by intensity(rate) and duration.
- Neither simple additive nor multiplicative models are sufficient to model the joint effect of smoking and radiation.
- The interaction effect appears to be larger at lower smoking rates than higher rates.

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Related Issues
Interpreting Site-Specific Risks

- Difficult to interpret and generalize effect modification
  - ERR gender effects mirror baseline gender effects, but baseline effects may be similar across populations
  - Age at exposure effects in the ERR may depend on birth cohort or period effects on baseline rates
  - Can also be problems in generalizing EAR patterns
- Site-specific differences in patterns are likely to exist
  - However much of observed variability is consistent with random variation
  - Formal statistical tests generally lack power to detect real differences
  - Statistical methods for shrinking estimates toward a central value are likely to lead to improved estimators of risk levels, gender effects and age-time patterns

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Adjusted Site-Specific Risk Estimates
A Simple/Simplistic Example

- LSS solid cancer mortality 1950 – 1997*
  - 86,572 in-city members of the LSS
  - 9,335 solid cancer deaths
    - ~440 associated with radiation exposure
- ERR model for all solid cancers with gender, attained age, and age at exposure effects (similar to incidence model)
- ERR models also fit for 18 specific "sites"
  - Site-specific ERR MLEs range from < 0.1 (oral cavity, pancreas, prostate) to 1 or more (breast, bladder, brain)
  - Estimated number of excess cases range from less than 3 (prostate oral cavity, cervix) to more than 80 (stomach, lung)

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Adjusted Site-Specific Risk Estimates
A Simple/Simplistic Example

- Use Bayesian methods to describe population mean and variance and produce adjusted site-specific risk estimates
  - "True" site-specific risk estimates taken as sample from a $N(\rho, \theta^2)$ distribution
  - Non-informative priors for ρ and θ^2
  - Posterior distributions for site specific risks and population parameters described using MCMC methods (WinBugs software) and summarized using the posterior mean values
- Simplifying assumption: effect modifiers have same form for all sites
  - Implies that only level of the risk (ERR) varies by site

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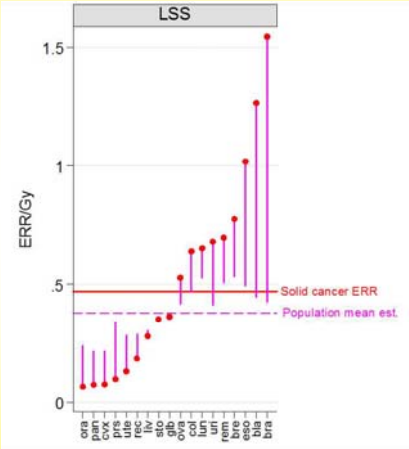
Adjusted Site-Specific Risk Estimates
A Simple/Simplistic Example



MLE's shown as red dots
vertical lines extend to posterior mean estimate

- Unadjusted estimates range from 0.06 to 1.6
- Adjusted estimates range from 0.2 to 0.5
- Considerable reductions for largest risk estimates
- Suggests that statistical uncertainties are relatively large
- More realistic approach would allow nature of effect modification to vary across sites
  - Complicates calculations and summarization

Summary and Conclusions

- Accumulating data and modern analytical methods make it possible to investigate radiation effect modification in some detail
- Data are limited even in the largest cohort
  - Especially true when modeling interactions
- Both ERR and EAR descriptions provide equally important and complementary information
  - Attained age is an important factor in both
  - Generalization of age at exposure and gender effects can be difficult
- Pooled analyses may be useful in looking at effect modification
- More work is needed to address issues related to the interpretation of site-specific risks

Acknowledgments

- We stand on the shoulders of giants
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- Collaborators
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Result
Fitting Models

	np	Deviance	p
Rad Only	19	9764.29	
Smk Only	22		
Additive	26	9412.82	<.001
GenAdditive	28	9404.05	<.001
Multipve	26	9410.16	<.001
GenMultipve	28	9400.66	<.001

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Selected References

- Detailed solid cancer incidence analyses
  Preston et al Radiat. Res. 2007 168:1-64
- Leukemia mortality analyses
  Preston et al Radiat. Res. 2004 162: 377-389
- Solid cancer mortality analyses
  Preston et al Radiat. Res. 2003 160: 381-407
- Lung cancer incidence analyses
  Furukawa et al Radiat. Res. 2010 174(1):72-82
- Adjusted site-specific risks
  Pawel et al Radiat. Res. 2008 169: 87-98
  Preston et al Radiat. Res. 2010 174:816-824
- Overview of RERF cohorts and dose estimates
  Cullings et al Radiat. Res. 2006 166:219-254

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